RECEIVED
OPPT CBIC

2003 JUL 11 PM 12:05

Thiuram Category Justification and Testing Rationale

Revised

CAS Registry Numbers 97-77-8, 97-74-5 and 137-26-8

Rubber and Plastic Additives Panel of the
American Chemistry Council
December 2001
Revised June 2003

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council includes the following member companies: Alco Chemicals; Bayer Polymers LLC; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and, R.T. Vanderbilt Company, Inc.

Summary

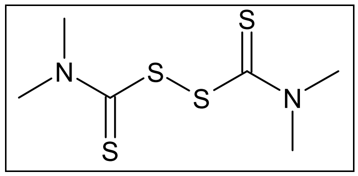
The member companies of the American Chemistry Council's RAPA Panel submit this revised test plan for the thiurams category for review and public comment under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program. A test plan and supporting documentation for the thiurams category was submitted on December 12, 2001 and included two chemicals (CAS numbers 97-77-8 and 137-26-8). The revised test plan incorporates data for a third member of the thiurams category (CAS number 97-74-5). Comments received from EPA and the public have been considered in the revised test plan.

Thiurams are used as primary accelerators in natural and synthetic rubbers. Their use in rubber products requires negligible water solubility, high organic/oil solubility, relatively low melting point and low vapor pressure. Existing data for members of this category indicate that they are of low concern for mammalian toxicity but toxic to aquatic organisms. The thiurams are biodegradable, so there is little concern for ecological persistence or bioaccumulation. They are of moderate concern for skin irritation and allergic skin reaction. The RAPA Panel concludes that there are sufficient data on the members of this category to meet the requirements of the EPA HPV Challenge Program and no additional testing is recommended.

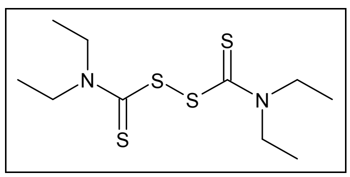
Thiuram category

As defined under the EPA HPV Challenge Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals and to avoid unnecessary testing.

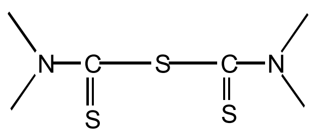
Based on EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following chemicals constitute the Thiuram Category:



tetramethyl thiuram disulfide
thiram
thioperoxydicarbonic diamide, tetramethyl-
137-26-8 (TMTD)



tetraethyl thiuram disulfide
thioperoxydicarbonic diamide, tetraethyl-
97-77-8 (TETD)



tetramethyl thiuram monosulfide
thiodicarbonic diamide ([(H2N)C(S)]2S), tetramethyl-
97-74-5 (TMTM)

Figure 1. Chemical structures

Structural Similarity. The materials in this category share the basic structure: two alkyl groups are attached to a nitrogen atom, which in turn is attached to a molecule of carbon disulfide. Two of these molecules are attached to each other through one or two sulfur atoms to form the thiuram mono- or disulfide respectively.

[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm.

Activity Similarity: The thiurams are fast-curing primary accelerators for natural and synthetic rubbers, speeding the formation of the sulfur crosslinks and donating sulfur to the rubber to form those cross-links. They are also secondary accelerators for thiazole and sulfenamide accelerators.

TMTD is used in agriculture as a fungicide; its generic chemical name is thiram. TETD is also a prescription drug used in the treatment of alcoholism; its brand name is Antabuse (generic name disulfiram).

Common Precursors: The thiurams are manufactured from a secondary amine (dimethylamine or diethylamine) and carbon disulfide to form a dithiocarbamate; two of these dithiocarbamate molecules are attached to each other using an oxidizer such as hydrogen peroxide.

Common Breakdown Products: All three thiuram sulfides degrade to their respective dithiocarbamates when exposed to heat or alkaline conditions and to carbon disulfide and amine in acid.

Table 1. Physico-Chemical Properties

Chemical **CAS#**	**Tetramethyl thiuram monosulfide (TMTM)** **97-74-5**	**Tetramethyl thiuram disulfide (TMTD)** **137-26-8**	**Tetraethyl thiuram disulfide (TETD)** **97-77-8**
Molecular Weight	208.37	240.4	296.66
Melting Point	101-112° C	145 - 155˚ C (decomposes)	64 - 73° C
Boiling Point	301.3° C (calculated)	129°C @ 20 mm Hg (decomposes)	117˚ C @ 17 mm Hg
Relative Density	1.38 g/cm^3	1.3 – 1.4 g/cm^3 @25˚C	1.3 g/cm^3
Vapor Pressure	2.7x10^{-4} hPa @ 25˚ C (calculated)	2.3x10^{-5} hPa @ 25˚ C	9.5x10-6 hPa @ 25° C (calculated)
Partition Coefficient (log Pow)	0.75 (calculated)	1.73	3.88
Water Solubility	15 mg/l @ 20° C	16.5 - 30 mg/l @ 20˚C	4.1 mg/l @ 25˚C

Similarity of Physicochemical Properties. The similarity of the physicochemical properties of these materials parallels their structural similarity. All are solids at room temperature with low vapor pressures, negligible water solubility, Log P values below 4, and subject to rapid hydrolysis.

Fate and Transport Characteristics. The thiurams decompose in water, especially under acidic or alkaline conditions. The presence or absence of light does not significantly alter the degradation rate, so additional photodegradation modeling is not proposed. These materials have been shown not to partition to water or air if released into the environment due to their low water solubility and low vapor pressure. Calculated Bioconcentration Factors and Log P values indicate that these materials are not Persistent Organic Pollutants (POPs). Additional computer-modeled environmental partitioning data is not proposed for the members of this category.

Toxicological Similarity. Existing published and unpublished test data for the thiurams demonstrate the similarity of these compounds.

Aquatic Toxicology. The thiurams are toxic to algae, water fleas and fish. For TMTD, the 96-hour EC_{50} for algal growth inhibition is approximately 1 mg/l (1 ppm); the 48-hr EC_{50} for *Daphnia* is less than 0.3 ppm; and the 96-hr LC_{50} for fish (bluegill) is approximately 0.1 ppm. Data from TETD and TMTM are in the same order of magnitude. Because acceptable data are available on all compounds, no additional ecotoxicity testing is proposed.

Acute Toxicity: Acute oral and dermal toxicity data are available for all three compounds. The acute oral LD_{50} for TMTM is 1320 mg/kg, for TMTD, 1080 mg/kg, for TETD, approximately 1300 mg/kg. The acute dermal LD_{50} for TMTM and TMTD is >2000 mg/kg; for TETD, 2050 mg/kg. The acute inhalation LC_{50} for TMTD is 4.4 mg/l. Acceptable data on two routes of exposure are available for all three compounds. Given their structural and biological similarity it is expected that the inhalation toxicity of TETD and TMTM would closely resemble that of TMTD. Because acceptable data are available on all compounds, no additional acute toxicity testing is proposed.

Mutagenicity: Bacterial reverse mutation assays, *in vitro* and *in vivo* chromosome aberration studies, and other *in vitro* and *in vivo* genetic toxicity studies have been conducted on all three members of the category. Positive and negative results have been observed in essentially all *in vitro* studies conducted on these compounds; further studies would likely do little if anything to resolve this issue. The results of *in vivo* mutagenicity studies are uniformly negative. The RAPA Panel concludes that the thiurams are weakly mutagenic when tested using *in vitro* methods and non-mutagenic using *in vivo* methods. Because acceptable data are available on all three compounds, no additional mutagenicity testing is proposed for these materials.

Repeated Dose Toxicity: Several 90-day subchronic toxicity studies and an 18-month carcinogenicity study have been conducted on TMTD. A 90-day study and a 2-year carcinogenicity study have been conducted on TETD. Fifteen-day, 28-day and 18-

month studies have been conducted on TMTM. These data should be acceptable to characterize the subchronic and chronic toxicity of these compounds. In addition, TETD has been used as a human drug for several decades with few adverse effects reported. Because acceptable data are available on all three materials, no additional subchronic or chronic toxicity testing is proposed.

Reproductive and Developmental Toxicity: Developmental toxicity data are available for all three materials; reproductive toxicity data are available for TMTD. The results of these studies show that none of these compounds are selective or specific developmental or reproductive toxins. Because acceptable developmental toxicity data are available on all three compounds and acceptable reproductive toxicity data are available on TMTD, no additional reproductive or developmental testing is proposed for these materials.

Conclusion: The physical, chemical, environmental fate and toxicological properties of the thiurams are similar and generally follow a regular pattern. Therefore, the EPA's definition of a chemical category has been met.

Test Plan: Table 2 provides the test plan for the thiurams category. TMTM, TMTD and TETD meet the EPA definition of a chemical category. Acceptable data on at least one member of the chemical category exist for environmental fate, aquatic toxicity, acute toxicity, repeated dose toxicity, mutagenicity, reproductive toxicity and developmental toxicity. In the case of TETD, human data are also available because of its use as a prescription drug. A thorough hazard analysis can be made with the data available; additional animal studies would not likely result in significant changes to what is already known about these products.

The RAPA Panel concludes that there are sufficient data on this category to meet the requirements of the EPA HPV Challenge Program, and no additional testing is recommended.

Table 2. Test Plan for the Thiuram Category*

Test	Tetramethyl thiuram monosulfide (TMTM) 97-74-5	Tetramethyl thiuram disulfide (TMTD) 137-26-8	Tetraethyl thiuram disulfide (TETD) 97-77-8
Physical/Chemical Properties			
Boiling Point	A	A	A
Melting Point	A	A	A
Vapor Pressure	A	A	A
Partition Coefficient	A	A	A
Water Solubility	A	A	A
Environmental Fate			
Hydrolysis	C	A	C
Biodegradability	M	A	M
Photodegradation	M	A	M
Fugacity	A	A	A
Aquatic Toxicity			
Acute Fish Toxicity	A	A	A
Acute Invertebrate Toxicity	A	A	A
Alga Toxicity	A	A	A
Mammalian Toxicity			
Acute Toxicity	A	A	A
Mutagenicity – gene mutation	A	A	A
Mutagenicity – chromosome aberration	A	A	A
Repeated Dose	A	A	A
Reproductive Toxicity	C	A	C
Developmental Toxicity	A	A	A

* see Table 1 for Physical and Chemical Property Data
Key for symbols in table:
A = Adequate data available
M = Modeling data available
C = Use of Category Approach

Background Information: Manufacturing and Commercial Applications

Manufacturing

The thiuram rubber accelerators have been manufactured worldwide for over 60 years. They are manufactured by batch rather than continuous process. Thiurams are manufactured by combining a secondary amine with carbon disulfide in alkaline aqueous solution, forming a dithiocarbamate salt. The salt is then oxidized, usually with hydrogen peroxide; two molecules of dithiocarbamate joining to form one molecule of thiuram.

Commercial Applications

The largest commercial use of the thiurams is as general purpose cure rate accelerators for natural and synthetic rubber vulcanization. Thiuram accelerators are typically used at 0.5 to 2 parts accelerator per every 100 parts of rubber (phr).

Shipping/Distribution

Thiuram-based compounds are shipped extensively throughout the world from manufacturing plants located in North America, South America, Europe, and Asia.

Worker/Consumer Exposure

The vast majority of thiurams is used by the rubber industry, mostly by large industrial users as ingredients for their rubber compounding processes.

The rubber and plastics additives industry has a long safety record and sophisticated industrial users handle these materials. These materials are available as pellets or powders; they are frequently treated with other materials to minimize dust generation. Most large industrial users also have mechanized materials handling systems, so exposure is expected to be minimal. The greatest potential for skin and inhalation exposure is at the packing station at the manufacturing site and, to a somewhat lesser degree during weighing at the customer site. Nuisance dust is the primary source of worker exposure.

Consumer exposure is minimal. Small amounts are used in rubber processing, and the materials themselves decompose or become bound in the rubber matrix during vulcanization. The most likely route of consumer exposure is skin contact from rubber or latex articles. Skin irritation, or possibly an allergic skin reaction may occur, but only in sensitive individuals subjected to prolonged and repeated exposure, especially under moist conditions.

TETD, TMTD and TMTM are regulated for use in food-contact applications by the Food and Drug Administration:

> 21 CFR 177.2600 (Rubber Articles intended for Repeated Use): As accelerator, not to exceed 1.5% by weight of rubber product
>
> 21 CFR 175.105 (Adhesives): no limitations

TMTD (thiram) is an EPA-approved fungicide (40 CFR 180.132):

> Sec. 180.132 Thiram; tolerances for residues.
>
> Tolerances for residues of the fungicide thiram (tetramethyl thiuram disulfide) in or on raw agricultural commodities are established as follows:
> 7 parts per million in or on apples, celery, peaches, strawberries, tomatoes.
> 7 parts per million in or on bananas, (from preharvest and postharvest application) of which not more than 1 part per million shall be in the pulp after peel is removed and discarded.
> 0.5 part per million in or on onions (dry bulb).

TMTD is a restricted-use pesticide; it is to be purchased and applied only by licensed professionals. It is not authorized to be sold to the general public.